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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) 02-465

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Nancy Joyce Simmons
(Printed Name of Person Sending Correspondence)

/nancy joyce simmons/
(Signature)

Application Number	Filed
10/632,054	July 31, 2003

First Named Inventor: Robert E. Richard

Art Unit	Examiner
1614	Alicia R. Hughes

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 29,674
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

/Rosemary M. Miano/
Signature

Rosemary M. Miano
Typed or printed name

908.518.7700
Telephone number

September 17, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[x] *Total of 1 forms are submitted.

REASONS FOR REQUESTING PRE-APPEAL REVIEW

1) Status of Claims

Claims 1, 3-13 and 15-30 are pending in the application and are presented for this Pre-Appeal Review.

2) The Provisional Non-Statutory Obviousness-Type Double Patenting Rejection is Erroneous

Claims 1, 3-13 and 16-18 are rejected on the ground of provisional non-statutory obviousness-type double patenting on the basis of (a) claims 1-23 of Strickler et al, U.S. Patent Application Serial No. 10/894,400 ("STRICKLER") and (b) claims 1 and 4-23 of Richard et al, U.S. Patent Application Serial No. 10/632,008 ("RICHARD I").

As an initial point, it is noted that this rejection is a *provisional* rejection and is thus not ripe for rational argument at this point because the claims of 10/894,400 have not issued. As noted in MPEP 804 I B (emphasis added): "Occasionally, the Examiner becomes aware of two copending applications…that would raise an issue of double patenting ***if one of the applications became a patent***. … The merits of such a provisional rejection ***can*** be addressed by both the applicant and the Examiner without waiting for the first patent to issue." Thus, Applicant has the right to address the provisional double patenting rejections at a later date, when and if the double patenting rejections are the only rejections remaining in the subject applications. See in particular MPEP 804.I.B.1:

> If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue. If both applications are filed on the same day, the examiner should determine which application claims the base invention and which application claims the improvement (added limitations). The ODP rejection in the base application can be withdrawn without a terminal disclaimer, while the ODP rejection in the improvement application cannot be withdrawn without a terminal disclaimer.

Moreover, with regard to the claim rejection based on claims 1-23 of STRICKLER, it is respectfully submitted that the claims of STRICKLER are directed to *radiation stable* copolymers and are thus the very antithesis of the polymers in the present claims, which are directed to homopolymers and copolymers that comprise *radiation sensitive* groups that undergo a reduction in molecular weight.

With regard to the claim rejection based on claims 1 and 4-23 of RICHARD I, it is respectfully submitted that the claims of RICHARD I pertain to a polymeric release region comprising a silicone copolymer comprising a plurality of siloxane units and a plurality of non-siloxane units. It is not seen how these claims are pertinent to those presently claimed, particularly since the claims of RICHARD I do not recite *radiation sensitive* groups. Indeed, one of the objectives of RICHARD I is to produce devices that are *radiation resistant* such that they can undergo radiation sterilization. See paragraph [0016].

In view of the foregoing, it is respectfully submitted that the double patenting rejections based on STRICKLER and RICHARD I are erroneous.

3) The Non-Statutory Obviousness-Type Double Patenting Rejection is Erroneous

Claims 1, 3-13, 16-18 and 30 are rejected on the ground of non-statutory obviousness-type double patenting on the basis of claims 1-24 of Richard et al U.S. Patent No. 7,241,455 (formerly cited as U.S. Patent Application Serial No. 10/409,358 ("RICHARD II").

This rejection is clearly erroneous. In this regard, Claim 1 of RICHARD II reads as follows:

> 1. An implantable or insertable medical device comprising (a) a therapeutic agent and (b) a polymeric release region that controls the release of said therapeutic agent upon administration to a patient, wherein said polymeric release region comprises **a radiation-crosslinked polymer that is crosslinked without a crosslinking agent**, wherein said radiation-crosslinked polymer is a radiation-crosslinked methylene-containing polymer that is formed from one or more hydrocarbon monomers and wherein said polymeric release region is crosslinked with a radiation dose of at least 10,000 rads. (emphasis added)

It is a basic tenet of polymer chemistry that crosslinking *builds molecular weight*. In contrast to RICHARD II, the present invention teaches the opposite, describing a polymer whose molecular weight is reduced by exposure to radiation.[1]

Thus, the double patenting rejection is in error and should be reversed.

4) The Rejection Under 35 U.S.C. § 103(a) Based on PHAN in View of CRUISE in View of PINCHUK and in View of FURST is Erroneous

The rejection of Claims 1, 3-13, 16-18 and 30 under 35 U.S.C. §103(a) based on Phan et al., U.S. Patent No. 5,674,242 (PHAN), Cruise, U.S. Patent No. 6,537,569 ("CRUISE"), Pinchuk et al, U.S. Patent Application Publication No. 2002/0107330 ("PINCHUK") and Furst, U.S. Patent Application Publication No. 2002/0099438 ("FURST") is erroneous.

35 U.S.C. §103 requires that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. MPEP 2141. " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), quoting *In re Kahn* , 441 F.3d 977, 988, (Fed. Cir. 2006).

None of the references alone or in combination teach or suggest the current invention, which contains a number of key concepts including:

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[1] As indicated in the instant specification, such a reduction in molecular weight is effected by chain scission. In the present claims, homopolymers and copolymers are included which comprise radiation sensitive groups. As noted in the specification, such groups represent weak links in the polymer chain, corresponding to expected scission points when the polymer chain is exposed to a specific dose of radiation. See paragraph [0037]. By coupling such radiation sensitive groups between polymer segments that are more radiation stable, the lower limit of molecular weight degradation can be effectively controlled. *Id.*

1) treating the release region with a radiation dose of at least 100,000 rads that is effective to reduce the molecular weight of the polymer and increase the cumulative release of said therapeutic agent in an amount of at least 10% subsequent to administration to a patient; and
2) using radiation sensitive groups (to create favored scission points for the polymer during the process of molecular weight reduction).

PHAN teaches an endoprosthetic device carrying a polymer member having an embedded therapeutic compound. The polymer member is formed of a shape-memory polymer for expansion upon exposure to a selected stimulus. PHAN teaches the use of UV light to cause crosslinking in a mixture of monomers comprising methyl methacrylate, polyethylene glycol methacrylate, butylenemethacrylate in a 2:1.5:1 ratio with a crosslinker such as hexanedioldimethyacrylate and a thermal or UV initiator such as benzoin methyl ether or azobisisobutylnitrile (see col. 6, lines 21-64). Example 2 of PHAN describes the extrusion of a blend of polyocetenylene, polyethylene glycol and triallyl isocyanurate (crosslinking agent) with the extruded product then being crosslinked by exposure to irradiation in the form of a 2.5 Mrad electron beam.

In contrast to the present invention, PHAN:

1) uses radiation to provide crosslinking (with the associated increase in molecular weight);
2) adds crosslinking agents that ensure such crosslinking (and thus increase molecular weight);
3) does not teach the polymers of the present invention; and
4) fails to describe how PHAN would achieve an increase the cumulative release of the therapeutic agent upon treatment with radiation, particularly in the face of PHAN's emphasis on crosslinking.

Again it is noted that the present invention employs radiation to *reduce* polymer molecular weight. As discussed in the instant specification, *scission* is the process whereby molecular weight is decreased, and in the invention as presently claimed, the polymeric release region is provided with a polymer that comprises radiation sensitive groups, thereby introducing favored scission points for the polymer during the process of molecular weight reduction. PHAN, in contrast to the present invention, uses radiation to *crosslink* the polymers described therein, a process that is well known to *increase* molecular weight, and thus teaches away from the invention.

The Examiner has pointed to paragraph [0029] of the specification, wherein it is noted that two basic reactions are believed to occur when a polymer is exposed to radiation:

> (1) chain scission (i.e., a random rupturing of bonds) of polymer molecules and (2) cross-linking of polymer molecules. Crosslinking generally results in the formation of larger, three-dimensional polymer structures. Chain scission, on the other hand, generally results in a decrease in the molecular weight of the polymer molecules. While polymers may display both types of reactions, one type of reaction will typically dominate. For increased release, it is preferred to use polymers in which chain scission reactions dominate. Chain scission is generally evidenced by a reduction in the molecular weight of the polymer (e.g., the weight-average or number-average molecular weight of the polymer) upon exposure to the radiation.

This would not appear to be controversial. For example, crosslinking would appear to generally result in an increase in the molecular weight (except, for example, in cases where chain scission overwhelms the effect of crosslinking), and chain scission would appear to generally result in a decrease in the molecular weight (except,

for example, in cases where crosslinking overwhelms the effect of chain scission). For this reason, for increased release, it is preferred to use polymers in which chain scission reactions dominate. Although not explicitly stated in paragraph [0029], it is also well-known in the polymer art that a reduction in polymer molecular weight (such as that achieved by radiation where chain scission dominates) results in an increase in the rate of therapeutic agent release from a polymeric matrix, whereas an increase in molecular weight (such as that achieved by radiation where crosslinking dominates) results in a decrease in release rate.

As presently claimed, the radiation must *unequivocally* (*cf.* preferentially in paragraph [0029]) reduce the molecular weight ("a radiation dose of at least 100,000 rads that is effective to … reduce the molecular weight of the polymer"). Thus, to the extent that chain scission and crosslinking might both occur, chain scission must dominate to meet the claim language.

Conversely, to the extent that chain scission might possibly occur simultaneously with the crosslinking processes described in PHAN, the effect of any such scission is clearly masked by the crosslinking processes. Otherwise, PHAN would not teach that the polymers described therein are "crosslinked to varying degrees so that the polymer will soften with heat but not flow." See col. 6, lines 14-16. In others words, the idea in PHAN is to fuse the polymer such that it does not flow.

The Examiner notes that 2.5 Mrads (of Example 2) read on the instant invention, which calls for a radiation dose that is at least 100,000 rads. The Examiner, however, further erroneously argues that "it logically follows that the same therapeutic agent comprising the same polymeric release region is used in the same host, subject to a radiation dose that gives the same effect to the same patient population (Please see Col. 6, lines 29-33)." In the present case, however, things can hardly be said to be "the same." For example, in the portion of PHAN cited, the polymers described are unrelated to those presently claimed (they are methacrylates). Moreover, PHAN includes a *crosslinker*, which is in direct conflict with the present invention, because crosslinkers promote an increase the molecular weight. Nor does PHAN teach or suggest a polymer that comprises radiation sensitive groups (in order to introduce favored scission points for the polymer during the process of molecular weight reduction), as this would be antithetical to crosslinking a polymer into a mass that does not flow.

The use of three other additional references to support this rejection do not make up for these deficiencies in PHAN.

CRUISE describes crosslinked hydrogels which have no relevance to PHAN, except, perhaps, to the extent that CRUISE, like PHAN, employs crosslinking. As noted for PHAN, crosslinking teaches away from the present invention, which is focused on *reducing molecular weight.* The Examiner's position that the hydrogel subject matter does not make any difference is without merit. One skilled in the art would not look to hydrogel chemistry to modify technology that does not even mention hydrogels.

CRUISE also does not teach that irradiating a polymer will increase the cumulative release of the therapeutic agent from the device, or that such irradiation would have any impact whatsoever on the release

kinetics of the device, although it is well known in the polymer art that an increase in crosslinking decreases release rate.

The citation of PINCHUK also does not make up for the preceding deficiencies in PHAN and CRUISE. As noted above, PHAN is directed to a crosslinked shape memory polymers and CRUISE describes crosslinked hydrogels. PINCHUK's composition comprises: (a) a biocompatible block copolymer comprising one or more elastomeric blocks and one or more thermoplastic blocks and (b) a therapeutic agent, wherein the block copolymer is loaded with the therapeutic agent. PINCHUK uses specific blocks of selected polymer types to achieve a desired combination of hardness and elasticity. There is no teaching or suggestion that the block copolymer compositions of PINCHUK could be used in PHAN or CRUISE or that the shape-memory polymers of PHAN or the hydrogel polymers of CRUISE could be used in PINCHUK.

It should be noted that PINCHUK does not teach or even suggest the use of any radiation treatment for any purpose at all. PINCHUK merely describes therapeutic agents being released over time. Thus PINCHUK does not make up for the above noted deficiencies in PHAN and CRUISE vis-à-vis molecular weight reduction and release rate enhancement as a result of radiation. Also, the attempt to combine a reference that does not even mention the use of any radiation treatment or the concept of crosslinking with a reference that uses radiation for crosslinking is without any foundation. Thus, one skilled in the art would not look to PINCHUK to combine with PHAN and CRUISE, and even if the references were combined, the present invention would not be achieved.

The final reference discussed in this rejection is FURST. FURST describes a stent treated with gamma, beta and/or e-beam radiation to reduce the vascular narrowing of a stented section (paragraph 21). FURST also teaches away from the present invention by using crosslinking (with the associated increase in molecular weight) to alter the release rate of biological agents (see paragraph 39). For example, FURST describes the crosslinking effect as partially or fully entrapping the salts of biological agents so that he agent takes a longer time to release (see paragraph 39). This is a clear teaching away from the current invention.

Moreover, the amount of radiation used in FURST is less than 2000 rads (paragraph 39), which is orders of magnitude below the minimum amount of 100,000 rads claimed in the present invention. Even the sterilization levels in FURST are described as less than 5000 rads (paragraph 41). It should also be noted that the 2000 rads is the upper limit of FURST and FURST even teaches away from the current invention by suggesting that lower amounts of radiation should be used (paragraph 39, last sentence). And again, as noted above, FURST teaches the use of radiation to effect crosslinking in order to decrease release rate, which is antithetical to the presently claimed invention.

For at least these reasons, the rejection under 35 U.S.C § 103(a) is in error and Claims 1, 3-13 and 15-30 are patentable over the cited references.